REMARKS

Applicant renews its previous request for favorable reconsideration, augmented by the further amendments above and these additional remarks. The contents of applicant's August 18th response are incorporated here by reference.

Claims 8 and 31 are amended presently, to further recite that the minicells are approximately 400 nm in diameter, with support in the specification and the present inventors' earlier PCT application, PCT/IB02/04632, cited in the present specification and relied upon by the present application to support the definition and purification methods of minicells. *See*, *e.g.*, page 4, lines 16 and 19; page 14, lines 13-14; page 29, line 22.

The '632 application, for instance, discloses that "[m]inicells are approximately 0.4 μm in diameter and, hence, do not permeate through a 0.2 μm pore size." Page 41, lines 21-22. In view of the uniform size of minicells, the '632 application further discloses that a 0.45 μm can be used to filter out parent bacterial cells. Page 43, lines 1-7. Likewise, the present specification discloses that the same 0.2 μm and 0.45 μm filters can be used for purification of minicells. Page 15, line 12, 13 and 20-22.

Entry of this revision is warranted because no new matter is introduced thereby. Upon such entry, claims 8, 10-15, 17, 18, 20-22 and 31-36 will be pending for consideration.

1. Size of Minicells

In the final Office action, Examiner Singh discounted applicant's previous arguments allegedly dependent on minicells' size, asserted that such features "are not recited in the rejected claims," and further recommended that applicant "amend the claims to limit the bacterially derived intact minicells to a 'specific size' in order to distinguish minicells of claimed method from the one known in prior art." Page 6, fourth to bottom line to page 7, line 3.

Without acquiescing to the examiner's reading of the claim language, applicant has amended claims 8 and 31 in a good-faith effort to address the examiner's stated concern. That is, applicant has further amended the subject claims to clarify that the minicells "are approximately 400 nm in diameter."

Accordingly, there can be no reasonable doubt that the cited reference, Sabbadini, does not teach or suggest the present claims because Sabbadini's "minicells" can have any size from about 0.005, 0.1, 0.15, 0.2 to about 0.25, 0.3, 0.35, 0.4, 0.45 or 0.5 micrometers (column 38, lines 30 and 31).

Moreover, as discussed in applicant's August 18th response (see page 7, fourth and fifth paragraphs), not only do Sabbadini's "minicells" have different sizes from the minicells of the present claims, Sabbadini's "minicells" embrace a whole genus of cell derivatives, such as membrane blebs, that are actually not minicells. For this reason alone, Sabbadini fails a Section 102 reference.

2. Generality of the Claimed Invention Across a Range of Small Molecule Drugs

In the final Office action, Examiner Singh remarked that applicant did "not provide an appropriate affidavit or declaration supporting that the specific limitations and conditions as set forth in argument is *effective* in delivering the drug to a target cells." Page 11, lines 15-17 (emphasis in original). During the September 17th interview, Examiner Singh further recommended the applicant's submission of evidence concerning the generality of the discovery, on which the claimed invention is based, across a range of small molecule drugs.

Applicant, once again, thanks Examiner Singh for recognizing the unexpected nature of the discovery. In this context, applicant submits concurrently an executed 37 C.F.R. § 1.132 Declaration. The Declaration demonstrates, with published and unpublished data, that a broad range of small molecule drugs can be loaded into minicells and that the resultant, small molecule drug-packaged minicells show significant anti-tumor efficacy.

As such, applicant believes that the Declaration adequately addresses the examiner's inquiries about (A) the claimed invention's *effectiveness* in delivering drugs to a target cell and (B) its *general* applicability across a range of small molecule drugs.

3. Small Molecule Drugs Do Not Encompass Therapeutic Nucleic Acids

Also during the course of the September 17th interview, Examiner Singh recommended that applicant further discuss the commonly understood meaning of "small molecule" and whether it encompasses therapeutic nucleic acids such as siRNA.

Applicant submits that "small molecule" and "small molecule drug" are well-understood and widely used phrases. For instance, the PubChem database, hosted by the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH), is a small molecule drug database. Thus, "PubChem … provides information on the biological activities of ***small molecules***" (http://pubchem.ncbi.nlm.nih.gov/help.html#fPubchem, last accessed December 5, 2010; emphasis added). In the same vein *The Genomic Glossaries*, maintained by the Cambridge Healthtech Institute, defines small molecule drugs as follows.

> **small molecule therapeutics, small molecules:** Low molecular-weight drugs. Compared to larger molecular weight pharmaceuticals such as proteins, peptides, and carbohydrates, small molecules can more easily penetrate cell membranes and the blood brain barrier. Can be delivered orally or intravenously. These molecules tend to incur lower process development and manufacturing costs.
>
> Preferred for drugs as they are orally available (unlike proteins which must be administered by injection or topically). **Size of small molecules is generally under 1000 Daltons, but many estimates seem to range between 300 to 700 Daltons**.

http://www.genomicglossaries.com/content/drug_discovery_gloss.asp, last accessed December 5, 2010 (emphasis in original and added). See also the United States Pharmacopeia publication entitled USP Guideline for Submitting Requests for Revision to *USP-NF V3.1 April 2007* - **SMALL MOLECULE DRUG** SUBSTANCES AND PRODUCTS, available at https://secure.usp.org/pdf/EN/USPNF/chapter1.pdf, last accessed December 5, 2010 (emphasis added).

It necessarily follows that "small molecule drug" is a well recognized term to describe a drug with a molecular weight generally under 1000 Daltons. By contrast, an siRNA molecule is about 20-25 nucleotides long and each nucleotide is about 330 Daltons. Accordingly, a 20-nucleotide siRNA is at least 6,000 Daltons, much larger than a small molecule drug.

From the foregoing, it is apparent that "small molecule" and "small molecule drugs" are well recognized terms in the art and they do not encompass therapeutic nucleic acids such as siRNA.

CONCLUSION

Again, favorable reconsideration of this application is requested, and Examiner Duffy is invited to contact the undersigned directly on any concern that she may have in this regard. Furthermore, the Commissioner is authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. If any extension is needed, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of the relevant fee(s) from the same deposit account.

Respectfully submitted,

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